

EXHIBIT 93

Retrospective Evaluation of Occupational Exposure to Organic Solvents: Questionnaire and Job Exposure Matrix

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Correct retrospective assignment of subjects to an exposure category is affected by a variety of problems: 1) lack of an objective lifetime measurement; 2) dependence upon the accuracy and thoroughness of the job description; 3) heavy reliance upon the knowledge of experts. The aim of the study was the quantification of the performance of a job exposure matrix (JEM) in evaluating solvent exposure, using expert judgements as the reference method. The sources of discrepancies between the two methods were analysed within the framework of two community-based case-control surveys. One included 765 cases of bladder cancer (BC) and 765 controls, the other 298 cases of glomerulonephritis (GN) and 298 controls. The JEM had been set up previously for a case-control study on laryngeal cancer and is based on 4000 discrete job titles.

Comparison between the JEM and expert exposure evaluation was carried out for 2736 job periods in the BC study and 929 in the GN study. Categories of exposure for both experts and JEM were dichotomized, using different cutoff points for exposure and non-exposure. Prevalence of exposure as assessed by the experts was twice as high in the GN study (19%) as in the BC study (10%), showing the importance of the questionnaire design and of the inclusiveness of the definition of exposure. Sensitivity of the JEM vis-a-vis the experts was low (23-63%), whereas specificity was rather high (87-98%). The best concordance between the two methods was obtained with a specific dichotomy from the JEM and a narrow definition of exposure by the experts. Bias and loss of power resulting from JEM misclassifications were calculated with a theoretical population odds ratio of 3 and an exposure prevalence of 10%. If the experts' classification of the subjects according to exposure is assumed to be 100% correct, using the JEM led to a bias in estimating the odds ratio, ranging from 1.5 to 2.1, and to a loss of power equivalent to a reduction in the number of subjects by a factor of 5 to 10.

Analysis of systematic discrepancies between exposure assessments of the experts and the JEM showed that they were clustered with some job categories and arose from different sources: 1) inadequate job descriptions, related to the codification system adopted and necessitating the gathering of information at the individual level; 2) true disagreements between JEM and experts regarding the definition of solvent exposure. These disagreements were analysed in detail and led, in some cases, to question the use of experts as a gold standard.

Organic solvents include a large variety of liquid compounds whose dissolving and volatile properties permit them to disperse or extract solids, resins, oils or other liquids. Approximately 100 different solvents are now in current use:¹ in paints, varnishes, glues, inks, dry cleaning and metal degreasing, in many chemical processes, in vegetable oil extraction and as carriers in pesticides, cosmetics and aerosols.

The widespread application and complex nature of solvents and the products in which they are found make it difficult to identify homogeneous groups at risk for any specific substance. Silica dust exposure, for example, concerns well-defined occupational groups, but practically everyone uses solvents in everyday life. In some occupational settings, solvent recovery processes are frequently employed to minimize vapour loss and make industrial operations economical; nonetheless, in many applications, workers remain exposed to high levels of solvents.² An additional complication is that the type of solvents used (and their handling conditions) for some pro-

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ducts, including paints and degreasers, have changed substantially over the past 50 years. Moreover, many solvents are petroleum-based products; the close relationship between these and other petroleum products such as fuel and gasoline or styrene (a monomer used in manufacturing polyesters) suggests that their impact on public health ought to be studied together.

These general considerations demonstrate the difficulties in comparing studies assessing solvent exposures. The large range of exposure prevalences observed among control groups in different case-control studies may result from disagreements among experts about the definition of solvent exposure and not simply from the consideration of different populations or periods of observation. For epidemiological purposes, the problem is the identification of populations whose exposure to solvents is significantly greater or different from that of the general population.

Job Exposure Matrices and Specific Questionnaires

Retrospective assignment of subjects to given chemical compound exposure categories is often effected by questionnaires followed by an expert judgement. Such an approach, which we will call *expert assessment*, is affected by a variety of problems: lack of an objective lifetime measurement; reliance on the judgement of experts; strong dependence on reported descriptions of jobs, economic activity and tasks. While it aims at optimizing the accuracy of job classification according to exposure, this procedure is time-consuming and expensive. Information bias may also be introduced when very detailed questionnaires which collect information on occupational tasks are administered to cases and controls whose willingness to collaborate may be affected by their health. This problem is particularly serious as it entails a differential misclassification by case-control status.

Job exposure matrices (JEM) would theoretically solve these problems; they could also be used when occupational histories are described only by job titles. In order to be applicable to any set of data, a complete JEM should include along the job axis all possible codes within the classification system adopted. There are 1506 job titles listed in the International Standard Classification of Occupations³ (ISCO) and 159 economic activities in the International Standard Industrial Classification⁴ (ISIC). A complete JEM based upon the combination of these two systems would include a very large number of couples, although many of the possible combinations ($1506 \times 159 = 239454$) are most unlikely. Differential misclassification is less likely to occur when a JEM is used, but the drawback is usually a substantial loss of information.

The relative effectiveness of a JEM as opposed to an expert assessment varies greatly depending on the chemical compound at issue.^{5,6} For organic solvents, because of their widespread use, exposure assessment by either method is very difficult. Certainty of exposure depends greatly on the job description. In a JEM, that description corresponds to the definition of a job title and is frequently insufficient to permit the assignment of an exposure category to the job. Another drawback arises because the investigator is often interested in evaluating the role of specific subgroups of solvent: their interchangeability in many applications means that misclassification between groups may be very high.

Objectives of the Study

The aim of the study was to quantify the performance of a JEM, in terms of relative sensitivity, specificity and potential bias, using expert assessment as a reference method in two community-based case-control surveys. In the absence of an objective measure of exposure, an in-depth interview and an exposure evaluation of each subject by experienced occupational hygienists, although subjective and not free from misclassification, presently provide the best results in the context of population-based case-control studies.⁷

Particular attention was given to the detection and analysis of the main discrepancies between the results of these methods. These disparities may arise from two distinct sources:

- 1) indirect exposure information, i.e. the job title, is not as complete as direct information about tasks actually executed and reported by subjects and does not take into account the variability of exposure between workers in the same job category;
- 2) disagreement between the group of experts who compiled the JEM and that which assessed exposure from questionnaires, regarding exposure assessment criteria, that is, what should be considered a solvent and the borderline between significant and negligible exposure.

METHODS

Description of the Job Exposure Matrix

A JEM⁸ was developed for an international case-control study on laryngeal cancer conducted in four countries of southern Europe. Subjects' occupational histories were coded according to two systems: ISCO for jobs and ISIC for economic activities. Each combination of codes was assessed by a panel of experts (referred to as the *JEM experts*), to determine exposure to 13 chemical compounds and three non-specific

exposures, including organic solvents. Exposure levels were defined as follow-:

- 10 non-exposed;
- 20 possibly exposed at low levels; intensity of exposure similar to that of some subgroups of the general population;
- 3x certain exposure of some members of this class at levels higher than the general population; insufficiency of job description does not permit a distinction between those exposed and those not exposed. This category is subdivided according to the a priori probability of exposure:
 - 31 probability $<1/3$;
 - 32 probability between $1/3$ and $2/3$;
 - 33 probability $>2/3$;
- 40 certainly exposed at levels clearly higher than the general population;
- 50 certainly exposed, and at levels known to be particularly high.

It should be emphasized that two separate concepts contribute here to defining exposure: the probability that a job entails exposure, and the intensity of exposure. In general, probability of exposure was given higher priority than intensity, so that any job causing possible exposure was classified 3x without consideration of the intensity. On the other hand, those certainly exposed were subdivided according to the intensity of their exposure. The JEM assigned exposure judgements to over 4000 discrete combinations of ILO-ISCO codes, abstracted from the occupational histories of more than 3000 individuals.

Description of the Bladder Cancer Case-Control Study

This case control study⁹ was carried out between 1984 and 1987. It included 765 cases and 765 hospital controls from five regions of France. The subjects' mean age was 63 and 86% of them were men. They were interviewed about their lifetime occupational histories using an open-ended questionnaire. For each occupation held for at least 6 months, they were asked about work assignments, including machines or products they had used, the percentage of time devoted to such use and dates of use. Industrial activity was coded according to a French classification and occupation according to ISCO. All interviews were reviewed blindly by a group of industrial hygienists, using a procedure first described by Gérin.¹⁰ They assessed the presence of chemicals to which the individual might have been exposed, from a list of 130 groups of substances, including five categories of solvents: oxygenated, halogenated, hydrocarbon, non-specified solvents and

petro-. Each compound was also assessed for reliability (presence possible, probable, certain), level (low, medium, high), and frequency ($<5\%$ of work time, $5-50\%$, $>50\%$). This assessment was based upon the subjects' reports as well as upon the long fieldwork experience of environmental monitoring experts.

To allow data linkage between the bladder cancer study and the JEM, the French classification of economic activities was translated into the international ISIC. Translation was possible for 90% of the jobs, so that 4438 job periods (defined as any period of continuous employment of at least 6 months in a given job category) representing 1954 different combinations of job and economic activity were available for study. Among those combinations, 800 also appear in the JEM, for a total of 2736 job periods. Exposure level was unknown for 24 job periods. For the 2736 job periods for which exposure had been assessed both by experts and matrix, we compared the results of the two methods. The distribution of job categories and the percentage of exposed subjects did not differ for those job periods available for the study and the 1702 which were excluded because they had not been assessed by the JEM.

Description of the Glomerulonephritis Case-Control Study

This study included 298 cases and 298 hospital controls between 1988 and 1990 in the Paris area. Subjects' mean age was 43 and 64% were men. Patients were interviewed about their lifetime occupational histories, using the questionnaire described above. Because the main hypothesis in this study involved solvents, specific questions about them were added. Chemists and industrial hygienists helped compile a detailed list of all tasks or products in which solvents could be found: adhesives, aerosols, chemical syntheses, chemical and pharmaceutical processes, cosmetics, degreasing and cleaning products, paint strippers, food and essence extraction, pesticides, printing inks and various types of surface coatings. With the aid of a structured questionnaire, interviewers were trained to reiterate this list in inquiring about each job period, and to record very detailed information, including the names of each product or process mentioned by the subjects (e.g. offset or gravure printing processes . . .), the technique by which the products were handled (brush, spray painting, soaking, robot) and the working conditions (indoor or outside work, use of solvent recovery processes, protective equipment). These questions also intended to allow non-experts to classify jobs as either certainly not exposed to any solvents or as possibly exposed to at least one.

Only these latter jobs were submitted to expert judgement, reducing the expense of employing experts. A total of 1600 job periods were described by the subjects, 426 of which included the handling of at least one product from the list. All of these job periods were reviewed blindly by two experts (the same ones as for the bladder cancer study), together with other jobs for which insufficient information had been obtained but which were known to entail frequent exposure. Sixty-five per cent of these 426 job periods were classified by the experts as possibly exposed to solvents. Solvents were placed into 30 chemical categories and coded to assess the reliability, frequency and level of exposure to the particular category(ies) and to solvents in general. Overall assessment was performed with a high sensitivity since occasional exposures, those which occurred less than once a month, and very low exposures were taken into account.

These 1600 job periods were composed of 875 different combinations of job and economic activity, coded according to ISCO and ISIC. Only 434 of these combinations were present in the JEM, so that 929 job periods were available for comparison of methods. The percentage of production jobs was higher among job periods available for the study (40%) than among those which were not (30%), and the percentage of exposed jobs was lower among the former (30%) than among the latter (44%).

Comparison of Solvent Exposure Assessment by JEM and Experts

Because lifetime occupational exposure assessment by both experts and the JEM was available for fewer than one third of the subjects, comparisons were carried out on job periods for all study subjects. In the JEM, exposure categories 20-33 combined degree and probability of exposure. In order to allow comparison of methods, JEM exposure categories were summarized as two dichotomous variables:

- 1) one maximally specific, i.e. only exposures assessed at 40 or 50 were classified as exposed ;
- 2) a maximally sensitive variable, i.e. only exposures assessed at a level of 10 were classified as not exposed, while those equal to or above 20 were classified as exposed.

In the glomerulonephritis study, expert evaluation was also coded in two ways: 1) broadly, i.e. including all exposures however minimal their level and their frequency; and 2) narrowly, where only regular exposures, i.e. those occurring at least monthly, at medium or high levels were considered, so that occasional or low exposures were classified as non-exposed.

Statistical Method

To quantify the performance of the JEM classification of exposure for the population of available job periods, where expert assessment is the reference, the following indices were calculated: sensitivity and specificity, which are not dependent on the frequency of exposure, and Kappa and Chi square of association, which do not depend on this frequency.⁵ Using a JEM instead of an expert evaluation is likely to increase misclassification of exposure, leading to a loss of power in the test and, even though non-differential, to a bias in the risk estimates towards unity. These effects were calculated in this study from the sensitivity and specificity values which correspond to different cutoff points for exposure and non-exposure for the JEM and the experts, and assuming that the subjects' classification by the experts was 100% correct. Those calculations were based upon a theoretical population odds ratio of 3, and assuming that 10% of the controls were exposed ($\alpha = 0.05$ and case-control ratio = 1). If p is the true exposure prevalence, OR is the true odds ratio, and Se and Sp are, respectively, the sensitivity and specificity of the JEM compared to the experts, then the modified OR_{JEM} can be derived by the following formula:⁷

$$OR_{JEM} = \frac{Se \cdot OR \cdot p + [1-Sp] \cdot [1-p]}{Se \cdot p + [1-Sp] \cdot [1-p]} \cdot \frac{[1-Se] \cdot p + Sp \cdot [1-p]}{[1-Se] \cdot OR \cdot p + Sp \cdot [1-p]}$$

The relative efficiency of the JEM compared to the experts was defined as the ratio of the sample size required to reach a power of 80% when using expert assessment to that required to reach the same power with the JEM.

RESULTS

Distribution of Job Periods According to Exposure Levels as Assessed by Experts and JEM

The experts found twice as many exposed jobs in the glomerulonephritis study as in the bladder cancer study, primarily because of a higher percentage of low level exposures (Table 1).

In both studies, there was a highly significant relationship between job distributions according to the exposure levels assessed by JEM and those evaluated by the experts. The higher the JEM exposure category, the higher the percentage of exposed jobs according to the expert assessment. In both studies, the percentage of high exposure jobs was greatest among jobs classified 50 by the JEM. However, there was an important percentage of jobs categorized by experts as non-exposed among those classified 40 by the JEM.

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TABLE 1 *Distribution of job periods according to exposure levels as assessed by experts and JEM*

Exposure categories	Non-exposed	(a) Bladder cancer study: exposure levels			(No.)*	Distribution of exposure categories
		Low	Medium	High		
10	96%	1%	2%	1%	(2235)	82%
20	92%	3%	4%	1%	(80)	3%
31	89%	4%	3%	4%	(134)	5%
32	70%	13%	18%	0%	(40)	1%
33	47%	7%	22%	24%	(76)	3%
40	58%	7%	19%	15%	(84)	3%
50	16%	13%	17%	54%	(63)	2%
Total	91%	2%	4%	3%	(2712)	100%

 $\chi^2 = 997, P < 0.001$

(b) Glomerulonephritis study: exposure levels					
Exposure categories	Non-exposed	Occasional or low	Regular and medium or high	(No.)*	Distribution of exposure categories
10	87%	8%	5%	(776)	84%
20	83%	14%	3%	(29)	3%
31	62%	29%	9%	(45)	5%
32	67%	11%	22%	(9)	1%
33	35%	24%	41%	(17)	2%
40	37%	13%	50%	(30)	3%
50	9%	13%	78%	(23)	2%
Total	81%	10%	9%	(929)	100%

 $\chi^2 = 279, P < 0.001$

* No. = number of job periods by exposure categories.

Overall Concordance between Experts and JEM Regarding Solvent Exposure Assessment

In both studies, the specificity of the JEM was rather good, around 90% when the dichotomy was sensitive and around 98% when it was specific (Table 2). Its sensitivity, on the other hand, was very low, ranging from 23% to 63%. The Kappa values were fairly low. It was lowest (0.29) in the glomerulonephritis study, when a broad definition of exposure by experts was associated with a specific dichotomy for the JEM and highest (0.45) when a narrow definition of exposure was considered for the experts and a specific dichotomy for the JEM.

Relative Efficiency of the JEM as Compared with Experts in Assessing Solvent Exposure

Taking the experts as the reference, and assuming their classification of the subjects' exposure was 100% correct, misclassification by the JEM led to a strong bias in the estimation of the odds ratio (Table 3). The number of cases and controls which would ensure an 80% power would therefore be much higher using a JEM instead of an expert assessment.

It is worth noting that improving sensitivity alone would not increase relative efficiency very much, even though lack of sensitivity was the chief weakness of the JEM evaluation. In both studies, relative efficiency did not increase using the maximum specificity or the maximum sensitivity dichotomy of the JEM, although sensitivity of the latter was nearly twice that of the former and specificity only 10% lower. This resulted from the assumption, in this exercise, of a low prevalence of exposure (10%), so that misclassification bias was primarily affected by lack of specificity rather than sensitivity.

Relative efficiency depended highly on the type of expertise. If a broad definition of exposure was considered, relative efficiency of the JEM was 12%; if a more narrow definition was considered, the relative efficiency increased to 18–26%, reaching this value when the JEM dichotomy was specific.

Analysis of the Sources of Discrepancies between Experts and JEM

Because JEM exposure categories 20 to 33 indicate probability of exposure, jobs classified as not exposed

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TABLE 2 Overall concordance between experts and JEM regarding solvent exposure assessment (all job periods)

	(a) Bladder cancer study				
	Experts	JEM (max. sensitivity)		JEM (max. specificity)	
		Non-exposed	Exposed	Non-exposed	Exposed
Non-exposed	2456	2140	316	2397	59 ^a
Exposed	280	105 ^a	175	187	93
Total	2736	2245	491	2584	152
% exposed	10%		18%		6%
Sensitivity			0.63		0.33
Specificity			0.87		0.98
Kappa			0.37		0.39
	(b) Glomerulonephritis study				
	Experts	JEM (max. sensitivity)		JEM (max. specificity)	
		Non-exposed	Exposed	Non-exposed	Exposed
Non-exposed	756	679	77	743	13 ^a
Exposed	173	97	76	133	40
Total	929	776	153	876	53
% exposed	19%		16%		6%
Sensitivity			0.44		0.23
Specificity			0.90		0.98
Kappa			0.35		0.29
	Expert narrow definition of exposure				
	Experts	JEM (max. sensitivity)		JEM (max. specificity)	
		Non-exposed	Exposed	Non-exposed	Exposed
Non-exposed	847	741	106	827	20
Exposed	82	35 ^a	47	49	33
Total	929	776	153	876	53
% exposed	9%		16%		6%
Sensitivity			0.57		0.40
Specificity			0.88		0.98
Kappa			0.32		0.45

^a Job periods with true disagreements between experts and JEM

by the JEM, when maximally specific, or classified as exposed by the JEM, when maximally sensitive, included combinations of job and economic activity in which only a certain percentage of jobs were exposed. Thus, true disagreements between experts and JEM existed only for those job periods in Table 2, indicated by ^a specifically:

(1) jobs classified 40 or 50 by the JEM and not exposed by the experts, i.e. 59 jobs out of 2736 (2.2%) in the bladder cancer study and 13 out of 929 (1.4%) in the glomerulonephritis study, when considering exposure as broadly defined by the experts;

(2) jobs classified 10 in the JEM and exposed by the experts, i.e. 105 jobs (3.9%) in the first study and 35 (3.8%) in the second, when considering a narrow definition of exposure by the experts.

As noted above, the primary weakness of the JEM evaluation was a lack of sensitivity, but lack of

specificity was also important in terms of relative efficiency. Since the JEM's lack of sensitivity/specificity may be clustered in a limited number of job situations or scattered over many of them, an analysis of agreement/disagreement by job category was performed.

In the bladder cancer study, 46% of the job periods involved production as did 86% of the exposed job periods. Most of the disagreements between experts and JEM concerned production workers.

Similarly, in the glomerulonephritis study, 41% of the job periods and 65% of the exposed job periods were production jobs. When the experts' broad definition of exposure was considered, 59% of the disagreements concerned production workers and 17%, service workers; when a narrow definition was considered, 80% of the discrepancies concerned production workers.

In both studies, most of the disagreements between the JEM, considered with maximum sensitivity, and

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TABLE 3 Relative efficiency of the JEM as compared with experts in assessing solvent exposure (assuming 10% of exposed subjects among controls)

	(a) Bladder cancer study		N ^c	N _{JEM} ^d	RE ^e = N/N _{JEM}
	OR ^a	OR _{JEM} ^b			
JEM (max. sensitivity)					
sensitivity = 0.63	3.0	1.6	96	472	0.20
specificity = 0.87					
JEM (max. specificity)					
sensitivity = 0.33	3.0	2.0	96	487	0.20
specificity = 0.98					
Expert broad definition of exposure	(b) Glomerulonephritis study		N	N _{JEM}	RE = N/N _{JEM}
	OR	OR _{JEM}			
JEM (max. sensitivity)					
sensitivity = 0.44	3.0	1.5	96	805	0.12
specificity = 0.90					
JEM (max. specificity)					
sensitivity = 0.23	3.0	1.8	96	831	0.12
specificity = 0.98					
Experts narrow definition of exposure			N	N _{JEM}	RE = N/N _{JEM}
	OR	OR _{JEM}			
JEM (max. sensitivity)					
sensitivity = 0.57	3.0	1.5	96	545	0.18
specificity = 0.88					
JEM (max. specificity)					
sensitivity = 0.40	3.0	2.1	96	372	0.26
specificity = 0.98					

^a OR, theoretical population odds ratio;^b OR_{JEM}, odds ratio given by the JEM;^c N, sample size required to detect a threefold risk with $\alpha = 0.05$, case/control ratio = 1, and power = 0.80 using expert assessment; the numbers refer to the N for cases and the N for controls.^d N_{JEM}, sample size required to reach a power of 80% using the JEM;^e RE, Relative efficiency = N/N_{JEM}.

the experts were clustered in four categories containing 25% of all production workers: metal industry workers (ILO codes 83 and 84), electrical and electronics workers, and plumbers and welders (Table 4). In the glomerulonephritis study, eight of the 11 blacksmiths and toolmakers were regularly exposed at a medium or a high level, but only two machinery fitters out of five, five electrical fitters out of 12, and four plumbers out of seven. Description of the specific tasks performed by these workers is given in the Appendix.

When the JEM was considered with maximum specificity, 73% of the disagreements in the bladder cancer study concerned four categories of workers: some textile and shoe workers, rubber and plastic products workers, and mechanics (Table 5). Under the broad definition of exposure in the glomerulonephritis study,

very few jobs among those classified 40 or 50 by the JEM were graded non-exposed by the experts. The only exceptions were rubber and plastic products workers and some categories of shoe workers. In this study, all mechanics were classified as regularly exposed at a medium or a high level.

DISCUSSION

In the bladder cancer study, a French system was initially used for coding the industrial activities; the recodification was time-consuming and expensive. The use of an international standard classification for jobs and industrial activities would greatly facilitate the exchange and comparison of methods.

There is, however, an additional technical problem involved in using this type of JEM: many combinations of job and economic activity are missing. In both

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TABLE 4 Main discrepancies between experts and JEM (considering a maximum of sensitivity for the JEM and a broad definition of exposure for experts)

ILO code	Job titles	Bladder cancer study			Glomerulonephritis study		
		Experts	JEM (max. sensitivity)		Experts	JEM (max. sensitivity)	
			Non-exposed	Exposed		Non-exposed	Exposed
83	Blacksmiths, toolmakers						
	Non-exposed	60	56	4	30	30	0
	Exposed	22	21 ^a	1	11	11 ^a	0
	Total	82	77	5	41	41	0
	% exposed	27%		6%	27%		0%
84	Machinery fitters and machine assemblers		Non-exposed	Exposed		Non-exposed	Exposed
	Non-exposed	55	28	27	7	6	1
	Exposed	56	11 ^a	45	19	5 ^a	14
	Total	111	39	72	26	11	15
	% exposed	50%		65%	73%		58%
85	Electrical fitters		Non-exposed	Exposed		Non-exposed	Exposed
	Non-exposed	51	47	4	18	17	1
	Exposed	9	8 ^a	1	12	12 ^a	0
	Total	60	55	5	30	29	1
	% exposed	15%		8%	40%		3%
87	Plumbers, welders . . .		Non-exposed	Exposed		Non-exposed	Exposed
	Non-exposed	60	60	0	14	14	0
	Exposed	12	11 ^a	1	9	7 ^a	2
	Total	72	71	1	23	21	2
	% exposed	17%		1%	39%		9%

^a Job periods with true disagreements between experts and JEM.

studies, these accounted for 40% of the job periods, which meant that the subjects' lifetime occupational exposures could not be analysed. As already mentioned, the huge number of possible combinations of job and economic activity makes it difficult to complete a JEM prior to data collection. But filling in the missing combinations as and when required for new studies is not a problem-free alternative, since exposure assessment methods may change substantially over time. In this regard, an interesting procedure has been described in which exposure levels were estimated for each occupation and industry separately¹¹ and then weighted for each job and industry combination. This technique may be very useful in the realization of a JEM.

In both of the studies reported here, overall concordance between experts and matrix was weak, when exposure assessment by both methods were summarized in dichotomous variables. However, it was highly dependent on the different dichotomies adopted for the two methods and was highest when a narrow

definition of exposure by the experts was associated with a specific dichotomy for the JEM. Curiously, the specificity of the matrix was high and the sensitivity low, although this JEM was set up with maximum sensitivity in order to estimate attributable risk.⁸ It should be pointed out that the JEM used seven categories of exposure while the experts used varying numbers of grades: concordance would undoubtedly have been much greater had the two methods not been treated as dichotomies, as suggested by the results in Table 1.

The higher percentage of exposed job periods found by the experts in the glomerulonephritis study compared to the bladder cancer investigation was very significant. While this difference may partly result from the fact that changes over time in solvent use were not taken into account, the relevant difference would be the recency of job periods rather than the age of the subjects. Nonetheless, we have verified that for all job periods of male subjects, from 1960 to 1980, the percentage of exposed jobs in the glomerulonephritis

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TABLE 5 Main discrepancies between experts and JEM (considering a maximum of sensitivity for the JEM and a broad definition of exposure for experts)

ILO code	Job titles	Bladder cancer study			Glomerulonephritis study		
		Experts	JEM (max. specificity)		Experts	JEM (max. specificity)	
			Non-exposed	Exposed		Non-exposed	Exposed
79	Tailors, dressmakers, sewers						
	Non-exposed	58	52	6 ^a	19	18	1 ^a
	Exposed	4	4	0	5	5	0
	Total	62	56	6	24	23	1
	% exposed	6%		10%	21%		4%
80	Shoemakers		Non-exposed	Exposed		Non-exposed	Exposed
	Non-exposed	9	4	5 ^a	2	0	2 ^a
	Exposed	9	0	9	3	0	3
	Total	18	4	14	5	0	5
	% exposed	50%		78%	60%		100%
84	Machinery fitters, mechanics		Non-exposed	Exposed		Non-exposed	Exposed
	Non-exposed	55	44	11 ^a	7	7	0 ^a
	Exposed	56	23	33	19	8	11
	Total	111	67	44	26	15	11
	% exposed	50%		40%			42%
90	Plastic products makers		Non-exposed	Exposed		Non-exposed	Exposed
	Non-exposed	12	1	11 ^a	6	3	3 ^a
	Exposed	4	0	4	0	0	0
	Total	16	1	15	6	3	3
	% exposed	25%		94%	0%		50%

^a Job periods with true disagreement between experts and JEM.

study, by social category, was still 50% higher than in the bladder cancer study. This result showed the importance of the type of questionnaire and criteria chosen by the experts in estimating prevalence of exposure. Specific questionnaires using the names by which tasks and products are known to workers certainly improve reporting, as was recently noted for various types of agents.¹² Nonetheless, the glomerulonephritis study's detailed questions about solvents seemed to increase the likelihood of detecting low and occasional exposures but did not significantly improve the detection of regular or high exposures.

One of the reputed advantages of matrices is that they lower the cost of collecting and processing information. This may be negated, as already noted,⁵⁻⁷ by the important bias in estimating odds ratios and the sizeable loss of power in the study due to misclassification. Thus relative efficiency should be taken into account in computing, a posteriori, the power of a given study using a JEM. However, JEM's relative efficiency compared with the experts was calculated assuming

that the latter were always correct. But misclassification errors attributed to the JEM in this study may be related to the loss of information resulting from the use of job titles instead of directly reported exposure information, but also to disagreements among experts regarding solvent exposure assessment criteria. The latter could tend to lower the observed relative efficiency if, in some cases, the JEM's apparent lack of sensitivity was in fact the experts' lack of specificity or its converse.

As a matter of fact, analysis of discrepancies between the exposure assessments of the experts and the JEM showed that they arose from various sources:

i) the choice of cutoff points between exposure and non-exposure for both methods;

ii) inadequacies in the job descriptions given by the ISCO and ISIC systems, necessitating additional information in order to assess exposure; for example, a pump attendant in a petrol station is considered a salesperson (number 45190) by ISCO and as involved in retail trade (economic activity 6200) by ISIC. Both

codes, obviously, were compiled for economic purposes and not for detecting exposure to hazardous or other substances.

iii) true disagreements among experts regarding the definition of solvent exposure, and the application of the definition to particular products, hence, concerning the existence of exposure and its intensity. Detailed analysis by job category showed that these true disagreements were clustered within some job categories rather than scattered over all jobs.

The group of scientists who constructed the JEM did not consider that some metal industry workers, such as toolmakers and machinery-fitters, were exposed to solvents, although subjects in both studies mentioned the use of degreasers. In the bladder cancer study, on the other hand, the JEM's apparent lack of specificity concerning mechanics was in fact a lack of sensitivity attributable to the experts analysing the questionnaires. They tended to rely too much on the subjects' statements, so that the one-quarter of mechanics who did not mention using solvents were classified non-exposed. In the glomerulonephritis study, where subjects were systematically asked about cleaning solvents, all mechanics mentioned exposure.

Disagreement in evaluating exposure for plumbers and welders was of a completely different nature and was mainly due to the system of job codification. A subject self-described as a plumber is coded as a plumber; nonetheless, he often engages in tasks in which solvents are involved, such as painting or glueing. When using matrices to estimate solvent exposure, it may be preferable in some cases to code the tasks described with different ISCO numbers, weighted by the time spent on each of them, instead of coding the job title.

Disparities concerning rubber and plastic workers arose from differences in the criteria for exposure. In the bladder cancer study, the experts considered that the only significant exposure was that to rubber and plastic fumes, whereas the JEM experts found solvent exposure equally significant.

Shoemakers classified as non-exposed by the experts used water-based rather than solvent-based glues.

The ability to distinguish people who have been exposed to solvents from those who have not depends primarily on two factors: the quality of expert knowledge and the accuracy and thoroughness of job descriptions. The comparison carried out in this

Chapter, between experts and JEM, and between the two studies involving the same experts but different kinds of questionnaires, is of great interest because it shows that, beyond the choice of methods, the definition of criteria for exposure is critical in estimating solvent exposure prevalence.

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APPENDIX

Description of tasks and exposure frequency and level as assessed by experts for the principal discrepancies between experts and JEM in the glomerulonephritis study

(Main jobs classified as certainly non-exposed by the JEM and for which at least one job was classified as regularly exposed at a medium or a high level by the experts)

Blacksmiths, Toolmakers and Machine-Tool Operators (Total number of jobs = 41; discrepancies = 8)

ILO	Job category	ISIC	Economic activity	N	n	Level	Frequency hours/week	Tasks
83410	Machine-tool operator	3813	Manuf. of structural metal products	2	2	medium	2-20	degreasing
83420	Lathe operator	3819	Manuf. of fabricated metal products	5	1	medium	<2	degreasing
83420	Lathe operator	3843	Manuf. of motor vehicles	2	1	medium	<2	degreasing
83430	Milling-machine operator	3710	Iron and steel basic industries	2	2	medium	<2	degreasing
83930	Locksmith	3811	Manuf. of cutlery, hand tools	1	1	medium	<2	painting
83960	Metal-press operator	3819	Manuf. of fabricated metal products	2	1	medium	<2	degreasing

Machinery fitters, Machine assemblers and precision instrument makers (Total number of jobs = 26; discrepancies = 2)

84185	Airframe fitter-assembler	3845	Manuf. of aircraft	3	1	medium	2-20	paint/degreasing
84985	Mechanical products inspector	3843	Manuf. of motor vehicles	3	1	high	<2	degreasing

Electrical fitters and Related Electrical and Electronics Workers (Total number of jobs = 30; discrepancies = 4)

85110	Electrical fitter	3831	Manuf. of electrical machinery	1	1	medium	<2	cleaning
85320	Electrical equipment assembler	3829	Machinery and equipment	1	1	medium	<2	painting
85330	Electronic equipment assembler	3832	Manuf. of radio, TV	6	1	medium	<2	cleaning
85330	Electronic equipment assembler	3851	Manuf. of measuring equipment	1	1	high	2-20	cleaning

Plumbers, Welders, Sheet-Metal and Structural Metal Preparers and Erectors (Total number of jobs = 23; discrepancies = 4)

87105	Plumber	5000	Construction	7	1	medium	<2	glueing
87370	Vehicle sheet-metal worker	3843	Manuf. of motor vehicles	2	1	medium	<2	cleaning
87440	Constructional steel erector	5000	Construction	2	1	medium	<2	painting
87450	Metal shipwright	3841	Ship building and repairing	1	1	medium	<2	degreasing